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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,953	02/13/2001	R. Sanders Williams	UTSD:674US/SLH	2337

7590 08/26/2004

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,953	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59,61,62 and 70* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59,61,62 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 59, 61-62 and 70 are pending.

Note that the Office action mailed 28 January 2004 is vacated. Thus, the applicants' Appeal Brief filed 28 June 200, which is based on said Office action, is not considered. The prosecution of this application is reopened. And, new ground rejection is set forth below.

Applicants' amendment to claims in "Appeal Brief" filed 28 June 2004, which cancels claims 1-58, 60 and 63-69 and 71-101, and applicants' request (filed 28 June 2004) for extension of time of two months and request (16 June 2003) for exertion of time of one month have been entered. The pending claims 59, 61-62 and 70 are examined in this Office action.

Declaration under 37 C.F.R. 1.131 and 1.132

The signed declarations under 37 C.F.R. 1.131 and 1.132 filed 24 February 2004 have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 59, 61-62 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 recites "modulating muscle cell growth"; the recitation is not clear as to whether or not the modulation refers to increasing or decreasing muscle cell growth. See also the claim item *a*), "muscle cell growth modulation". Also, claim 59 is indefinites in the recitation "a small molecule modulator" because specification does not define said recitation; does it refer to any molecules ranging from inorganic molecules to organic compounds including small ribonucleic acid and small nuclear ribonucleoproteins? Further, the term "MCIP1" needs to be fully spelled out, otherwise it renders the claim indefinite. The dependent claims are also rejected.

Claim 61 recited that "small molecule modulator is an *agonist*" while claim 62 sets forth that "small molecule modulator is an *antagonist*". The claim recitations are not apparent as to whether or not the said small molecule can act as both agonist and antagonist at same time for said muscle cell growth.

Claim 70 recites "a second pharmaceutical agent"; the recitation is unclear regarding whether or not the said pharmaceutical agent comprises the modulator of claim 59. Does said second pharmaceutical agent differ from the first pharmaceutical agent? Additionally, claim 70 is unclear as to whether or not said second pharmaceutical agent is co-administered with the first pharmaceutical agent.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 59, 61 and 70 are rejected under 35 U.S.C. 102 (b) as being anticipated by Medina J. et al. (*Biochem. Pharmacol.* (1996) 59, 1459-1466).

Medina et al. teach a method of regulating muscle cell growth in a human subject (i.e., human blood vessel smooth muscle cells) comprising selecting cyclosporin A as a modulator for the said muscle cell growth, wherein cyclosporin is a *calcineurin* inhibitor wherein calcineurin is an activator for induction of MCIP1 (myocyte-enriched calcineurin-interacting protein) expression, and administering cyclosporin to a subject, i.e., the cultured human blood vessel smooth muscle cells (see Figure 1 and pages 1460-1461), as applied to the instant claim 59.

Medina et al. teach that the cyclosporin induces human pulmonary artery muscle cell proliferation (see abstract, and Figure 1), which anticipates the instant claim 61.

In Figure 5, Medina et al. teach the said method further comprising administering to said subject a pharmaceutical agent (i.e., Sandostatin) other than the cyclosporin, which anticipates the instant claim 70.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 59, 61-62 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chin, E. R. et al. (*Gene Dev.* (1998) 12, 2499-2509).

Chin et al. teach a process of modulating skeletal and cardiac muscle cell growth comprising selecting a mammal (rat) subject, selecting a small molecule (i.e., cyclosporin) for calcineurin which is an active regulator for muscle cell growth, and administering the cyclosporin A to the subject (see abstract and pages 2502-2503, the section "*administration of the calcineurin antagonist cyclosporin A to intact animal promotes slow-to-fast fiber transformation*"). The Chin et al. teaching is applied to the instant claim 59.

In Figure 4, Chin et al. show that cyclosporin A has reciprocal effects on muscle cell growth through reducing slow myosin expression and enhancing fast myosin expression (see also the left column at page 2503), which is applied to the instant claims 61 and 62.

Please note that the current invention is directed to a method of modulating muscle cell growth by administering to a subject a polypeptide modulator but NOT to a method of modulating MCIP1 expression, and that the modulator-mediated regulation of MCIP1 is regarded as a mechanistic step, which is *an inherent property of calcineurin action*. Thus, the Chin et al. teachings are applicable to the above-mentioned claims.

Also, Chin et al. suggest administering calcineurin antagonist cyclosporin A (a pharmaceutical agent) to intact animal including human (see pages 2505-2506), and suggest that the process stated-above has a medical application, *e.g.*, treating cardiac hypertrophy, a cardiac disease (see page 2506). The Chin et al. teaching is thus applied to the instant claim 70.

Chin et al. do not explicitly teach that the subject of above motioned process of modulating muscle cell is a *human* subject.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to readily applied the Chin's method to the human subject because Chin et al. reference has suggested that the therapeutic agent (e.g., cyclosporin A) capable of modifying calcineurin activity selectively in skeletal muscles can be used in human subjects (see the left column, lines 1-3 at page 2507). Also, Chin et al. teach that a signaling pathway involved in mammalian skeletal muscle growth is cyclosporin-sensitive (see abstract). Thus, the skilled artisan would have applied the Chin's method to regulate muscle cell growth in a human subject and would have successfully arrived at the current invention. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Claims 59, 62 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sussman M. A. et al. (*Science* (1998) 281, 1690-1693).

Sussman et al. teach a process of modulating cardiac muscle cell growth comprising providing a small molecule inhibitor for calcineurin, i.e., cyclosporin, and administering the cyclosporin to a subject, e.g., transgenic mice (see abstract, Figures 1-2, and pages 1690-1691 and 1693), wherein calcineurin is an activator for induction of MCIP1 (myocyte-enriched

calcineurin-interacting protein) expression, and cyclosporin is an inhibitor (i.e., antagonist) of the calcineurin for muscle growth (see page 1690, the right column, the last paragraph). Note that calcineurin is an active regulator for muscle cell growth. Thus, the Sussman et al. teachings are applied to claims 59 and 62 of the current application.

Further, Sussman et al. teach that the cyclosporin therapy for cardiac disease, e.g., cardiac hypertrophy, (see page 1690 and the last paragraph of 1693), which is applied to claim 70 of the current application.

Sussman et al. do not explicitly teach that the subject is a human subject.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to readily applied the Sussman's method to the human subject because Sussman et al. reference has suggested that cyclosporin treatment of muscle growth-related hypertrophy (see Figure 1) is applied to human subject (see abstract, the last sentence), and suggested that the said treatment is of potential therapeutic for certain forms of human heart disease (see abstract). Thus, the skilled artisan would have applied the Sussman's method to regulate muscle cell growth in a human subject and would have successfully arrived at the current invention. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Claims 59 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuentes, J. J. et al. (*Hum Mol Genet.* 2000 July 1; 9(11):1681-1690) taken with Sussman M. A. et al. (*Science* (1998) 281, 1690-1693).

Fuentes et al. teach a method of using a small molecule, i.e., calcium, to induce DSCR1 gene expression through a *calcineurin*-dependent mechanism (see figures 3 and 7,and page 1687, the right column, the 2nd paragraph), wherein calcium regulates the DSCR1 expression in a human subject, e.g., human SH-SY5Y cell (see Figure 7, and page 1687, the right column, the 2nd paragraph), and calcium is administered (introduced) through a calcium ionphore into the human subject by calcium ionphore (see "*Materials and Methods*" section at page 1688). The Fuentes et al. teaching is applied to the instant claim 59.

Please note that Fuentes et al. have taught (i) the DSCR1 protein sequence (see Figure 4) which reads on the sequence of myocyte-enriched calcineurin-interacting protein (MCIP1), (ii) the DSCR1 is a *calcineurin* (subunit A) *binding protein* (see page 1682, the left column, the 2nd paragraph, and abstract) and negatively regulates *calcineurin signaling* in mammals (see page 1682, the left column, the 2nd paragraph) thereby regulates muscle growth.

In the Fuentes' reference, calcium acts as an agonist for the muscle cell growth; thus, the Fuentes' teachings are applied to the instant claim 61.

Fuentes et al. do not expressly teach a method of regulating muscle cell growth in the said human subject.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to select calcium as a modulator and administer the said modulator to the human subject for modulation of muscle cell growth because the DSCR1 directly interacts with (regulates) *calcineurin* which is a crucial signaling intermediate in regulation of skeletal muscle growth. The Fuentes' method would have inevitably led to modulation of the muscle cell growth

via DSCR1/*calcineurin* signaling pathway, and thus the above Fuentes' method is an obvious variation of the claimed method of the current application as applied to the instant claim 59. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed.

Prior Art

The prior art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

(1) Yang, J. et al. (*Cir. Res.* (2000) 87, e61-e68) teach calcineurin is an activator for induction of MCIP1 expression.

(2) Berchtold, M. W. et al. (Physiol. Rev. (2000) 80, 1215-1265) teach (i) a role of calcineurin in regulating muscle cell growth, e.g., selectively upregulating slow skeletal muscle fiber expression and inhibition of calcineurin leading to a slow-to-fast muscle fiber transformation; (ii) calcineurin is a calcium/CaM-dependent phosphates is a mediator of calcium-dependent signaling determining skeletal fiber type gene expressions (see pages 1246-1247); and (iii) FK506 and cyclosporin bind and inhibit calcineurin activity

(3) Palleja, X. E. et al. (US Pat. No. 5869318) teach a polynucleotide encoding the DSCR1 protein and amino acid sequence of the DSCR1 (i.e., MCIP1) protein.

(4) Dunn, S. E. ("*Calcineurin and skeletal muscle growth*" (2002) *Nat. Cell Biol.* 4, E46-E47) teach a crucial role of calcineurin in the regulation of muscle cell growth and demonstrates cyclosporin A and FK506 inhibitory effect on the calcineurin.

(5) Colao, A. et al. (*J. Clin. Endocrinol. Metab.* (1999) 84, 17-23) teach that treatment of a cardiovascular disease, e.g., left ventricular systolic function with Sandostatin (i.e., octreotide) drug.

(6) Vega, R. B. et al. (*Proc Natl Acad Sci U S A.* (2003) 100, 669-674) teach that MCIP expression is up-regulated by calcineurin sigling (see page 669, the right column, the 2nd paragraph).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Weber, Jon, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel W. Liu, Ph.D.

August 17, 2003

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER